REMARKS

Claims 1, 3-6, 8, 10, 11, 14-23, and 24 have been canceled and new claims 29-51 added. Each of the canceled claims (except claim 9) has been re-written as a new claim. The following table shows relationship between the canceled and new claims.

Presently Canceled Claim	New Claim
1	29
3-6	31-34
8	35
10	36
11	37
14-23	38-47
24	30
25	48
26	49
27	50
28	51

New claims 29-51 find support throughout the instant disclosure including the claims and Drawings as filed originally. No new matter has been added.

Particular support for language relating to functional fragments in new claims 29 and 30 can be found at pgs. 17-18, bridging paragraph; pgs. 20-21, bridging paragraph; and pg. 22, lines 21-24, for instance.

A. Claim Objections

Claim 1 was objected to on grounds that "APC" in step c should spell the abbreviation the first time it is used. The claim has been canceled. However, the requested change has been made to new claims 29 and 30.

Claims 3 and 6 stand rejected as being in an improper dependent form. The claims have been canceled in favor of new claims 31 and 34, respectively. It is believed that the new claims should address the objections.

Claim 4 was objected to as also being in an improper dependent form. The claim has been canceled and re-written as new claim 32. With respect to new claim 32, claim 29 (from which cl. 32 depends) is not limited to an ex vivo approach as alleged at pg. 3 of the Action. Applicants' specification provides for *ex vivo* and *in vivo* embodiments of the claimed method. See Applicants' specification at pg. 10, lines 1-19. Accordingly, there would be no basis for objecting to claim 32 on this basis.

Claim 5 was objected to as also being in an improper dependent form. The claim has been canceled in favor of new claim 33. However, Applicants respectfully disagree with the rejection on grounds that the Office is reading unrecited language into the claims. Applicants' specification at pg. 10, lines 1-19, for example, teaches that the claimed method can be practiced *in vivo* and *ex vivo* as needed. Thus, there would be no basis for objecting to claim 33 on this basis.

Claim 8 was objected to for reasons set forth on pg. 3 of the Action. The requested change has been made to new claim 35.

Claims 26 and 27 stand rejected for reasons mentioned at pgs. 3-4 of the Action. The claims have been canceled and rewritten as new claims 49 and 50, respectively. The phrase "or an artificial graft" has been removed from new claim 49.

In view thereof, Applicants submit that all claim objections have been addressed.

B. Rejections under 35 USC §112, second paragraph.

Claims 1, 3-6, 8-11, and 14-28 stand rejected as being unclear for reciting "functional fragment". The claims have been canceled and rewritten as new claims as shown in the Table above. New claims 29 and 30 have been written to feature more specific functional fragments.

Claims 1 and 24 stand rejected as being vague and indefinite for reciting "early graft failure". The claims have been canceled in favor of new claims 29 and 30. With respect to the new claims, Applicants respectfully disagree with the rejection on grounds that the phrase would be abundantly clear to one working in this field. For instance, pg. 1 of the application (lines 29-33) defines "early graft failure" not only temporally and physiologically but also with reference to late graft failure. Thus, there is no basis for the position that "early graft failure" is at all unclear.

Claims 1 and 24 stand rejected as being vague and indefinite for reciting the phrase beginning with "provided". While Applicants respectfully disagree with the rejection as formulated, the claims have been canceled in favor of new claims 29 and 30. It is believed that the new claims address the rejection.

Claims 1 and 24 stand further rejected on grounds that "and step a) of the method" is vague and indefinite. The claims have been canceled in favor of new claims 29 and 30. Basis for the rejection has been addressed.

Claims 1 and 24 stand further rejected on grounds that "the APC" is unclear. While Applicants must disagree that the phrase is at all unclear in view of the specification, basis for the rejection has been addressed by this submission. In particular, claims 1 and 24 have been rewritten as new claims 29 and 30, respectively.

Claims 1 and 24 stand rejected as being vague and indefinite on grounds that recitation in step c) of "increasing the APC sufficient to treat the graft" is unclear. While Applicants must

respectfully disagree, basis for the rejection has been addressed by canceling the claims in favor of new claims 29 and 30. As recited, the agent increases APC in the graft cells to treat the early graft failure.

Claim 8 was rejected as being vague and indefinite. While Applicants respectfully disagree, basis for the rejection has been addressed by canceling the claim in favor of new claim 35.

The rejection of claims 9 and 21 as being vague and indefinite have each been addressed. Claim 9 has been canceled. Claim 21 has been rewritten as new claim 45.

Claim 24 was rejected as vague and indefinite on grounds stated at pgs. 5-6 of the Action, bridging paragraph. Basis for the rejection have been addressed by this submission.

In view thereof, it is submitted that all outstanding rejections under 35 USC §112, second have been addressed. Reconsideration and withdrawal of the rejection are requested.

C. Rejections Under 35 USC §112, first paragraph (written description)

Claims 1, 3-6, 8-11, and 14-28 stand rejected on grounds that (Action at pg. 7):

> the specification fails to teach genuses of functional fragments for EPCR and NF-KB inhibitor or TM and which fragment qualifies as functional, and thus, the specification fails to provide an adequate description for what is now claimed

Applicant respectfully disagrees with the position taken for reasons of record. However in the interest of furthering prosecution, claims 1, 3-6, 8-11, and 14-28 have been canceled in favor of the corresponding new claims identified in the table shown above.

In particular, new claims 29 and 30 now feature more specific functional fragments of TM, EPCR, and NK- κB. Examples of such fragments and/or methods for testing for such functional fragments are disclosed throughout the instant specification. Reconsideration and withdrawal of the rejection are respectfully requested.

Applicants respectfully disagree with the rejection on further grounds.

In the present Action, the Office cites *In re Soll* (said to be a chemical case from 1939) to support the present rejection. Applicants note that the field of the present invention is not chemistry and so the relevance of the CCPA case is not understood. Even if the case is relevant however, it should not be allowed to pre-empt much more recent guidance from the Federal Circuit regarding the written description requirement. That guidance includes the *Vas-Cath* case (holding that correct inquiry for satisfying the written description requirement is "possession") and in the Federal Register, Vol. 66, pp. 1099-1111, part IB at pg. 1105 ("Guidelines"). See the Response filed on July 11, 2003 (discussing how the specification satisfies the written description request).

It is believed that new claims 29 and 30 fully satisfy the written description requirement set forth by the Guidelines and the Federal Circuit. Accordingly, there would be no basis for the Office making a written description rejection against the new claims.

In particular, each of new claims 29 and 30 feature functional fragments having a specific activity in a defined assay. Methods for testing fragments for functionality are disclosed throughout the application including references cited therein. Thus, Applicants have fully satisfied the "possession" standard set forth by the Guidelines and Federal Circuit.

In view thereof, it is submitted that all outstanding rejections under 35 USC §112, first paragraph (written description) have been addressed. Reconsideration and withdrawal of the rejection are requested.

D. Rejections Under 35 USC §112, first paragraph (enablement)

As an initial matter, Applicants gratefully acknowledge withdrawal of the rejection mentioned at pg. 9 of the Action.

Turning to the remaining basis for rejection, the Office cites Skolnick et al. (TIBTECH 2000 Jan; 18: 34) to support the position that Rudinger et al. is not too old and out of date to use as a basis for rejecting the claims. Respectfully, Skolnick et al is not relevant to the present rejection at all.

As understood, the cited portion from Skolnick et al. discloses problems encountered with the genome-sequencing project in which some have found it difficult to assign function to a sequence encoded by newly identified genes. See pg. 34 of the reference in particular. Those problems are not relevant to the claimed invention. Cited sequences in the pending claims are well known structurally and functionally. Accordingly, Skolnick et al. as relied on by the Office is not germane to the rejection.

More specifically, each of the TM, EPCR, and NF-κB sequences recited in the claims is known. Each has been described in detail in the specification including the references cited therein. Biological functions of each protein and preferred functional fragments have also been disclosed. Methods for obtaining and testing each has also been reported and referenced in the specification. In marked contrast, the function of many of the gene sequences described by Skolnick et al are apparently not known. Thus,

the problems related by Skolnick et al. are simply not relevant to the Office's enablement inquiry.

Accordingly, Applicants respectfully maintain that Rudinger is not germane to the instant rejection for reasons already mentioned. It is almost 30 years old and cannot outweigh more recent advances in the field of the claimed invention. The Office's citation of an unrelated reference should not change this view.

Nevertheless, it is believed that the present disclosure satisfies the "how to make" and "how to use" requirements of the statute, particularly in view of new claims 29 and 30.

E. Rejection Under 35 USC §102

Applicants gratefully acknowledge withdrawal of this rejection by Dr. Li.

F. Rejection Under 35 USC §103

Claims 1, 3-6, 8-11 and 14-28 stand rejected as being obvious under French et al. (USP 6,290,949), Fukudome et al. (USP 5,852,171), taken with Thomas, Stephens and Larson references. Applicants respectfully traverse.

It is well settled that the USPTO bears the burden of providing some teaching, suggestion or motivation in the cited references to make the claimed invention. See, for example, *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed.Cir.1999)):

> **our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references.**

See also *In re Dance,* 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed.Cir.1998); *In re Fine,* 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed.Cir.1988); and *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.,* 229 F.3d 1120, 1124-25, 56 USPQ2d 1456, 1459 (Fed.Cir.2000).

The CAFC decisions are abundantly clear. In the absence of some teaching, suggestion or motivation in the cited references to make the claimed invention, there is no basis for rejecting the claims under §103. Respectfully, that burden has not been met in this case and the rejection should be withdrawn.

In particular, the Office contends that Fukudome teaches that EPCR and TM "share the same function in activating cell protein C and both are down regulated during an inflammatory response such as exposure to TNF (abstract)". Action at pg. 11. Applicants have reviewed the cited portion of Fukudome and do not share the Office's reading of the Abstract.

As understood, the Fukudome abstract discloses that the RNA message encoding TM and EPCR are both down-regulated during TNF exposure. The similarity of that response does not mean that the functions of the proteins are the same as alleged by the Office. Those working in this particular field would know they are not the same. Indeed, TM is thought to be protein expressed on the lining of blood vessels that binds circulating thrombin. In contrast, EPCR is thought to be a receptor protein that binds a completely different protein (protein C). See Applicants' specification at pg. 2, lines 1-12 (TM); and pg. 20, lines 4-21 (EPCR) for a review. Accordingly, it is not seen how the Office can allege that the functions of TM and EPCR are the same when the proteins themselves would be understood to be so different. A worker reading the Fukudome abstract would understand and appreciate this distinction.

Further, the Office alleged that Fukudome "teach that both TM and EPCR decreased during inflammation....". Respectfully, the cited portion of Fukudome has been misread.

According to the Fukudome abstract, TM and EPCR function and RNA message can both be down regulated during exposure of endothelium to tumor necrosis factor (TNF). That limited disclosure says nothing about the TM and EPCR proteins themselves or what the levels of those proteins might be during inflammation.

On these grounds alone, no *prima facie* case has been made and the rejection should be reconsidered and withdrawn. The cited part of Fukudome, when taken alone or in combination with the other cited references, does not teach, suggest or provide any motivation to combine TM and EPCR according to the claimed invention.

Applicants respectfully disagree with the rejection on further grounds.

The French patent discloses a large list of gene sequences that reportedly can be combined with the gene therapy methods taught by the patent. Such sequences are diverse and include thrombin inhibitors, platelet inhibitors, growth factors, antioxidants, ribozymes and antisense RNAs targeted against particular proteins, receptor proteins, calcium channels, cholesterol modulating enzymes, and others. French at cols. 16-17, bridging paragraph. The gene therapy methods disclosed by French are also taught to involve an extensive list of possible gene sequences that includes TM and many other sequences. French at col. 5, lines 38-59.

It is not seen how a worker reading French (alone or in combination with the cited portion of Fukadome and the other references) could reasonably conclude that TM could be used with EPCR or the NF-KB inhibitor to resist early graft failure (claim 29) or to engineer a vascular graft (claim 30) with any expectation of success. If anything, the worker may have tried to use TM with one of the many other sequences reported by French which, as acknowledged by the Office, does not include EPCR or IKB. Fukadome taken alone or with any of the other cited references fails to remedy this deficiency. At most, the Fukadome patent teaches modulating EPCR itself as the basis for treating certain diseases. See Fukadome at col. 2 under "Summary

of the Invention". There is simply no specific teaching or suggestion in the cited references to use TM with EPCR or the NF-RB inhibitor as Applicants have done.

Applicants respectfully submit that what the Office has done is engage in "hindsight reconstruction" of the claimed invention. This approach has been expressly forbidden by the Federal Circuit. In the instant case, the Office has not pointed to any explicit teaching, suggestion or motivation to make the claimed invention in view of the art cited. On this basis alone, no *prima facie* case has been made and the rejection should be withdrawn.

It is believed that the application is in condition for allowance, which action is earnestly solicited. Although it is not believed that any fee is needed to consider this submission, the USPTO is authorized to charge our deposit account no. **04-1105** should such fee be deemed necessary.

Respectfully submitted,

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By: _____

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